CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761202Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Biosimilar to US-licensed Lucentis

Recommendation: Approval

EXECUTIVE SUMMARY

BLA 761202
Review Number: First round
Review Date: September 16, 2021

Drug Name/Dosage Form	Byooviz (ranibizumab-nuna) injection, for intravitreal use
Strength/Potency	0.5 mg/0.05 mL (10 mg/mL)
Route of Administration	Intravitreal injection
Rx/OTC dispensed	Rx
Indication	All indications currently approved for US-licensed Lucentis (0.5 mg/0.05 mL strength): Neovascular (Wet) Age-Related macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), and Myopic Choroidal Neovascularization (mCNV)
Applicant/Sponsor	Samsung Bioepis Co., Ltd

Product Overview

Byooviz (ranibizumab-nuna, SB11) is a recombinant humanized IgG1κ isotype monoclonal antibody F(ab') fragment developed as a biosimilar to US-licensed Lucentis (ranibizumab). Ranibizumab- nuna binds to the receptor binding site of all human alternatively spliced Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells resulting in the reduction of endothelial cell proliferation, vascular leakage and new blood vessel formation. Ranibizumab-nuna drug product is manufactured to have the same strength, dosage form, formulation, presentation and route of administration as the 0.5 mg/0.05 mL strength of US-licensed Lucentis in single-dose vial. Byooviz is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution for intravitreal injection supplied in single-dose glass vials containing ranibizumab-nuna at 0.5 mg/0.05 mL.

Quality Review Team

Discipline	Reviewer	Office/Division
Drug Substance/Drug Product/Immunogenicity	Jens Fricke	OBP/DBRR1
Comparative Analytical Assessment	Jens Fricke	OBP/DBRR1
OBP Labeling	Vicky Borders-Hemphill	OBP/IO
Drug Substance Microbiology/Facilities	Lindsey Brown	OPMA/DBM
Drug Product Microbiology/Facilities	Wendy Tan	OPMA/DBM
Facilities Assessment Lead	Zhong Li	OPMA/DBM

Microbiology Quality Assessment Lead	Maxwell Van Tassell	OPMA/DBM
CMC RBPM	Anh-Thy Ly	OPRO/DRBPM1
Application Technical Lead	Willie Wilson	OBP/DBRR1
OBP Review Chief	Qing Zhou	OBP/DBRR1
OBP Biosimilar Program and Policy	Marlene Schultz-DePalo	OBP/IO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Lois Almoza	ORO/DROSM
Signatory Authority	Wiley Chambers	OSM/DO
Cross-disciplinary Team Lead	Bill Boyd	OSM/DO
Clinical Reviewer	Lucious Lim	OSM/DO
Nonclinical	Maria Rivera	ORDPURM/DPTRDPURM
Clinical Pharmacology	Amit Somani	OCP/DIIP
Biostatistics	Yushuf Sharker	OB/DBIV
OSE/DMEPA	Otto Townsend/Nasim Roosta	OMEPRM/DMEPAI
OSI Consult	Ling Yang	OSI/DCCE/GCPAB

1. Names:
    a. Proprietary name: Byooviz
    b. Trade name: Byooviz
    c. Non-proprietary name: ranibizumab-nuna
    d. CAS registry number: 347396-82-1
    e. Common name: SB11 (Company Code), WB007 (CMO Code)
    f. INN Name: ranibizumab
    g. USAN Name: ranibizumab
    h. OBP systematic name: MABFRAG HUMANIZED (IGG1) ANTI P15692 (VEGFA_HUMAN) [SB11]
2. Pharmacologic category: Therapeutic recombinant humanized monoclonal antibody Fab fragment biosimilar.

Submissions Reviewed:

Communication	Date
761202/1 (Original Submission)	9/17/2020
761202/2 Response to OPMA Information Request #1	10/29/2020
761202/3 Response to OPMA Information Request #2 (Inspection status of (b) (4))	10/30/2020
761202/5 Response to OPMA Information Request #3	11/6/2020
761202/6 Response to OPMA Information Request #4 (Inspection status of (b) (4))	11/19/2020
761202/8 Response to OPMA Information Request #5 (Inspection status of (b) (4))	12/9/2020
761202/10 Response to OBP Information Request #6	1/8/2021
761202/11 Response to OPMA Information Request #7	1/8/2021
761202/13 Response to OBP Information Request #8	2/8/2021
761202/14 Response to OPMA Information Request #9	2/17/2021
761202/15 Response to OPMA Information Request #11	3/8/2021
761202/17 Partial Response to OBP Information Request #10	3/12/2021

761202/20 Partial Response to OBP Information Request #12	4/2/2021
761202/18 Partial Response to OBP Information Request #13	3/17/2021
761202/19 Partial Response to OBP Information Request #13	3/24/2021
761202/21 Response to OPMA Information Request #14	4/5/2021
761202/22 Response to OPMA Information Request #15	4/9/2021
761202/23 Partial Response to OBP Information Request #12	4/15/2021
761202/24 Response to OBP Information Request #16	4/16/2021
761202/25 Response to OPMA Information Request #17 (Inspection status of (b) (4))	4/16/2021
761202/26 Response to OPMA Information Request #18	4/29/2021
761202/27 Partial Response to OBP Information Request #10	4/30/2021
761202/28 Response to OBP Information Request #19	5/3/2021
761202/30 Response to OBP Information Request #20	5/14/2021
761202/30 Response to OPMA Information Request #21	5/14/2021
761202/31 EU inspection history for DS and DP sites	5/19/2021
761202/33 Response to OBP Information Request #22	5/25/2021
761202/32 Email Correspondence by SB11 US Agent for PLI	5/25/2021
761202/34 Copy of Letter to Janet Woodcock regarding PLI	5/28/2021
761202/36 Postmarking Commitment Submission Dates	7/13/2021
761202/38 Response to OBP Information Request #23	8/25/2021
761202/39 Response to OBP Information Request #24	8/27/2021
761202/40 Response to OBP Information Request #25	9/1/2021
761202/41 Response to OBP Information Request #26	9/3/2021
761202/42 Response to OPMA Information Request #27	9/14/2021
761202/43 Response to OPMA Information Request #27 (track change)	9/15/2021

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF#	DMF type	DMF Holder	Item Referenced	Code[1]	Status[2]	Date review completed	Comments (status)
(b) (4)	III		(b) (4)	3	N/A	N/A	None
	V			3	N/A	N/A	None

(b) (4)	III	(b) (4)	3	N/A	N/A	none

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There are enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.
None

3. Consults: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761202 for Byooviz (ranibizumab-nuna) manufactured by Samsung Bioepis, Co., Ltd. The data submitted in this application are adequate to support the conclusion that:

- The manufacture of Byooviz is well-controlled and leads to a product that is pure and potent;
- The comparative analytical data supports a demonstration that ranibizumab-nuna is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components.

It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Summary of Complete Response Issues:
N/A

C. Approval Action Letter Language:

- Manufacturing location
  - Drug Substance: (b) (4)
  - Drug Product: (b) (4)

- Fill size and dosage form: 0.5 mg/0.05 mL single-dose vial
- Dating Period:
  - Drug Product: 30 months at 5 ± 3°C, protected from light
  - Drug Substance: (b) (4) months at (b) (4)
  - For packaged products: Not packaged
- For stability protocols:
  - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug product and drug substance under 21 CFR 601.12.
- Exempt from lot release: Yes
  Note: Byooviz is exempted from lot release per FR 95-29960.

D. Benefit/Risk Considerations:

Byooviz (ranibizumab-nuna, SB11) is a proposed biosimilar to US-licensed Lucentis for the same indications as for the 0.5 mg/0.05 mL strength of US-licensed Lucentis (i.e., Neovascular Age-Related Macular Degeneration, Macular Edema following Retinal Vein Occlusion, and Myopic Choroidal Neovascularization). To support the demonstration that Byooviz is highly similar to US-licensed Lucentis, Samsung performed a comparative analytical assessment of SB11 and US-licensed Lucentis. As part of the comparative analytical assessment, the molecular attributes of ranibizumab were collectively assigned to appropriate assessment categories and a sufficient number of lots of each product were evaluated. A comprehensive array of analytical methods was used to support a demonstration that the products are highly similar. Each method was demonstrated to be suitable to detect and/or quantitate potential differences in critical quality attributes between SB11 and US-licensed Lucentis. The comparative analytical assessment data provided support the conclusion that Byooviz is highly similar to US-licensed Lucentis.

The overall control strategy for Byooviz manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, release and stability testing ensures process consistency, and drug substance and drug product that have appropriate quality and are free of adventitious agents. Drug substance and drug product facilities operate in compliance with cGMP and are acceptable for manufacturing.

E. Environmental Assessment or Claim of Categorical Exclusion:

A claim of categorical exclusion from environmental assessment (EA) according to 21 CFR 25.31(g) was provided and is acceptable.

F. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

1. Perform real-time drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at regular intervals through the end of shelf life. The study results will be updated annually in the

BLA Annual Report. The final results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

2. Provide bioburden test method suitability data for in-process samples from at least one additional lot of SB11 drug substance.

II. Comparative Analytical Assessment

I. Comparative Analytical Assessment Overview and Conclusions

Samsung Bioepis Co., Ltd (Samsung) is seeking licensure for SB11 as a biosimilar to US-licensed Lucentis. US-Lucentis is licensed in 0.3mg (6mg/ml) and 0.5mg (10mg/ml) strengths, in single-use vial and single-use pre-filled syringe. Samsung is seeking licensure for the 0.5mg (10mg/ml) strength in a single-use vial. Samsung performed a comparative analytical assessment (CAA) using 27 lots of US-licensed Lucentis (10 mg/mL) and 13 lots of SB11 (10 mg/mL). The SB11 lots evaluated included 6 process performance qualification (PPQ) drug substance (DS) lots, 1 pilot-scale drug product (DP) lot, 3 clinical DP lots, and 3 PPQ DP lots. SB11 DS lots were manufactured at (b) (4). SB11 DP lots were manufactured at (b) (4) All SB11 DP lot included in the CAA were independent of the DS lots evaluated. The SB11 clinical lots included in the CAA were used during the in vivo toxicology study (Lot P74602A) and the comparative clinical study SB11-G31-AMD (Lots P74604A and P74605A). The CAA included the following analyses to support a demonstration that SB11 is highly similar to US-licensed Lucentis:

- Extensive comparative physicochemical and functional assessments of quality attributes.
- Comparative assessments of the degradation profiles under forced degradation conditions. Studies included the evaluation of 1 SB11 clinical DP lot, 1 US-licensed Lucentis lot.

Samsung used a risk-based approach for the statistical evaluation of the analytical results:

- High risk-ranked quality attributes, denoted as "Tier 1", were tested using quantitative assays and were evaluated by equivalence testing.
- Moderate risk-ranked quality attributes, denoted as "Tier 2", were tested using quantitative assays and were evaluated by a quality range (QR) approach, for which the ranges were established based on the results derived from up to 26 US-licensed Lucentis lots. The upper and lower bound limits of the QR were estimated using a standard deviation multiplier (SDM) of 2.5 or 3.0. The SDM used to establish each QR was scientifically justified.
- Low risk-ranked quality attributes, denoted as "Tier 3", were tested using quantitative and qualitative assays and were evaluated using side-by-side visual comparison.

All analytical methods used during the CAA were performed at Samsung Bioepis Co. Ltd (Incheon, South Korea, FEI: 3010031951), except for several higher order structure analyses (i.e., secondary/tertiary structure, protein folding and aggregate characterization) which were performed at (b) (4)

(b) (4). Results from method validation, qualification and verification studies were provided and adequately support the suitability of each method for its intended use during the CAA.

Samsung also provided a comparison of stability studies under forced degradation conditions of thermal stress (40°C), pH (9.0 and 4.0), oxidative and photo stress conditions. The comparative forced degradation studies support that SB11 and US-licensed Lucentis have a similar degradation profile.

Based on our assessment of the SB11 and US-licensed Lucentis data, the results support a demonstration that SB11 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components. Samsung used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of SB11 and US-licensed Lucentis to support a demonstration that SB11 is highly similar to US-licensed Lucentis. The number and type of lots tested and data analysis methods were appropriate to allow for a meaningful evaluation of the results of the CAA. While differences were observed in a limited number of attributes, these do not preclude a demonstration that SB11 and US-licensed Lucentis are highly similar. Refer to Section V – Same Strength(s) below for addition comments regarding the comparison of strength, dosage form and route of administration between SB11 and US-licensed Lucentis.

II. Comparative Analytical Assessment Results

Table A. Quality Attributes Analyzed to Support a Demonstration of Highly Similar

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar
Primary Structure	Molecular weight	Yes
	Amino acid sequence	Yes
	N-terminal sequence	Yes
	C-terminal sequence	Yes
	Peptide mapping	Yes
	Disulfide bond	Yes
	Free sulfhydryl group	Yes
	Non-canonical amino acid	Yes
	Extinction coefficient	Yes
Post-translational Modifications	Oxidation	Yes
	Deamidation	Yes
	Acetylation	Yes
	Glycation	Yes
Higher Order Structure	Secondary structure	Yes
	Tertiary structure	Yes
	Protein folding	Yes
	Thermal stability	Yes
	Aggregates	Yes
	Protein size	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar
Purity and Product-related Variants or Impurities	Charge variants	Yes
	Isoelectric point	Yes
	High molecular weight (HMW) species	Yes
	Low molecular weight (LMW) species - Fragmentation	Yes
	Hydrophobic variants	Yes
Bioactivity	VEGF-A 165 binding	Yes
	HUVEC anti-proliferation (VEGF-A 165)	Yes
	VEGF-A 165 neutralization	Yes
	VEGF-A 121 neutralization	Yes
	VEGF-A 165 neutralization (VEGFR1)	Yes
	VEGF-A 110 binding	Yes
	VEGF-A 121 binding	Yes
	VEGF-A 189 binding	Yes
	VEGF family binding specificity (VEGF-B, C, D, and PIGF-1,2)	Yes
Drug Product Attributes	Protein concentration	Yes

Comparative assessment of the forced degradation stability studies was performed to evaluate potential differences in the degradation profiles between SB11 and US-licensed Lucentis when stored under thermal stress (40°C), basic stress (pH 9.0), acidic stress (pH 4.0), oxidative stress and photo stress conditions. Results support that the degradation pathway and rates of degradation between SB11 and US-licensed Lucentis are similar when stored under each condition.

III. Comparative Analytical Studies to Support the Use of a Non-US-Licensed Comparator Product

Not applicable.

IV. Assessment of Comparative Analytical Study Results

Quantitative Assessment of Analytical Study Results

All quality attributes evaluated using equivalence testing and QR met the comparative analytical acceptance criteria, except for the following:

1. **Protein concentration:** Comparative analytical results (n = 6 SB11 lots) for protein concentration measured by UV/Visible spectrophotometry show that one SB11 PPQ DP lot 00001 (9.4 mg/mL) exceeded the 9.5 – 10.5 mg/mL QR. All other SB11 lots were

within the QR. The magnitude (0.1 mg/mL) by which the DP lot exceeded the QR is minor and did not correlate with changes to biological activity. Samsung noted that the protein concentration result for SB11 PPQ DP lot 00001 meets the (b) (4) mg/mL protein concentration acceptance criterion described in the US-licensed Lucentis Certificate of Analysis and the proposed SB11 DP lot release acceptance criterion. Overall, the magnitude by which SB11 PPQ DP lot 00001 exceeded the protein concentration QR is minor and does not preclude a demonstration that SB11 is highly similar to US-licensed Lucentis.

V. Same Strength(s)

SB11 has the same dosage form and route of administration as US-licensed Lucentis. Samsung is seeking licensure of 0.5 mg/0.05 mL (10 mg/mL) in a single-use vial. US-licensed Lucentis is approved in this strength in a single-use vial. The 0.5 mg/0.05 mL strength of both SB11 and US-licensed Lucentis vial presentations are manufactured at a target 0.23 mL fill volume to ensure the consistent withdraw and intravitreal delivery of 0.05 mL drug product solution (0.5 mg label claim) using a 5-micron sterile filter needle, 1 mL Luer lock syringe and 30-gauge sterile injection needle. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. SB11 DP manufacturing process development data were assessed to confirm the suitability of the vial fill weight control strategy to consistently fill vials with sufficient volume to ensure the withdraw and delivery of the 0.5 mg label claim. Based on the comparative analytical assessment and manufacturing data, the proposed presentation of SB11 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Lucentis (0.5 mg/0.05 mL (10 mg/mL)).

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other notes
VEGF-A 165 binding (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.	(b) (4)	N/A

(b) (4)

HUVEC anti-proliferation (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.		N/A
VEGF-A 165 neutralization (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.		N/A
Identity	Safety and Efficacy	Intrinsic to the molecule.		N/A
High Molecular Weight (HMW) species/ Aggregates (product-related impurities)	Efficacy and Safety/ Immunogenicity	Manufacturing process and exposure to heat, basic, and light stress Minimal change is expected during storage under recommended conditions through expiry.		N/A

(b) (4)

Low Molecular Weight Species (Fragments) (product-related impurities)	Efficacy	Manufacturing process and exposure to heat, basic and oxidative stress. Minimal increase in fragments is expected during storage under recommended conditions.		N/A
Oxidation of Heavy Chain in CDR Region (Met34 and Met83)	Efficacy	Exposure to oxidative stress		Met34 and Met83 oxidation is not detected at release and is not impacted under process-relevant stress conditions.
Protein Content (mg/mL)	Efficacy	Manufacturing process		N/A
Osmolality	Efficacy	Formulation process		N/A
Appearance (color and clarity)	Efficacy and Safety	Formulation, contamination, or degradation		N/A
pH	Efficacy and Safety	Formulation process		N/A
Polysorbate 20 content	Efficacy and Safety	Intrinsic to DS and DP formulation		N/A

B. Drug Substance [ranibizumab-nuna] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

Category (type)	Risk	Origin	Control Strategy	Other notes
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	Production cell line	(b) (4)	N/A
Host Cell DNA (process-related impurity)	Safety	Production cell line		N/A
(b) (4) (process-related impurity)	Safety and Immunogenicity	Process-related impurity leached (b) (4)		N/A
(b) (4) (process-related impurity)	Safety, immunogenicity	Cell bank cryopreservation medium or culture medium		Worst-case (b) (4) clearance studies support the exclusion of in-process and release testing. Worst-case (b) (4), assuming no clearance, is below the Acceptable Daily Intake (ADI).
Leachables (process-related impurity)	Safety	Manufacturing components and the DS container closure system		N/A

			(b) (4)	
Microbial Enumeration (Bioburden)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process		N/A
Bacterial Endotoxins	Safety	Raw materials, manufacturing process		N/A

- **Description (ranibizumab-nuna):**

  Ranibizumab-nuna (SB11) is a recombinant humanized IgG1 kappa monoclonal antibody fragment manufactured in *E. coli*. SB11 is composed of one light chain (214 amino acid residues) linked by a C-terminal disulfide bond to one heavy chain (231 amino acid residue). The total molecular weight of SB11 is 48 kilodaltons. The complementarity-determining regions of SB11 is 100% identical to US-licensed Lucentis and facilitates binding to the receptor binding site of all human alternatively spliced Vascular Endothelial Growth Factor-A (VEGF-A) isoforms. SB11 harbors no glycosylation site and does not contain the mis-incorporation of non-canonical amino acids.

- **Mechanism of Action (MoA):**

  VEGF-A is a key driver of vasculogenesis and angiogenesis upon binding to its receptors, Flt-1 (VEGFR-1) and kinase insert domain receptor (KDR) (VEGFR-2), on the surface of endothelial cells. Binding of VEGF-A to its receptors leads to endothelial cell proliferation, neovascularization, and vascular leakage. The biological activity of VEGF-A is associated with Neovascular (Wet) Age-Related macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), and Myopic Choroidal Neovascularization (mCNV). The clinical efficacy of SB11 for these indications is mediated by binding to VEGF-A which neutralizes interaction with VEGFR-1 and VEGFR-2.

- **Potency Assay:**

  VEGF Binding Assay

  Potency of SB11 DS is assessed using a quantitative ELISA-based binding assay which utilizes 96-well plates coated with recombinant human VEGF (rhVEGF). Serial dilutions of SB11 test articles, reference standard and assay control are captured by the rhVEGF-coated plates. The current SB11 assay control (LCS-P02) represents US-licensed Lucentis lot 308120 which was

appropriately qualified against the reference standard in 2018 using size variant, charge variant, protein concentration and biological activity specifications. VEGF binding is measured by absorbance at 450 nm wavelength following the sequential addition of anti-human IgG (Fc-specific)-peroxidase antibody, TMB substrate and 1 N sulfuric acid. Data are fit using a 4-parameter logistic model. Relative VEGF binding activity of test articles is reported relative to the reference standard.

VEGF Neutralization Assay

Potency of SB11 DS is assessed using a quantitative cell-based assay (96-well plate format) that measures the ability of SB11 to attenuate VEGF receptor-mediated intracellular signaling in an engineered cell line, NFAT-RE-Luc2P/KDR 293 cells. The cell line is engineered to express cell-surface KDR (VEGFR2) and contains an NFAT-driven luciferase gene. The NFAT-RE-Luc2P/KDR 293 cells are appropriately qualified and cell culture maintenance is appropriately controlled through cell viability and cell passage limit. Binding of VEGF-A to the KDR-expressing cells triggers a Ca2+ signaling cascade resulting in NFAT-driven luciferase gene expression, which is quantitated by a plate reader upon addition of Steady-Glo luciferase solution. The VEGF neutralization assay measures the level of luminescence reduction correlated with the ability of SB11 test articles, reference standard and assay control (LCS-P02) serial dilutions to block VEGF-A binding. Data are fit using a 4-parameter logistic model. Percent neutralization is inversely proportional to the luminescent signal. Relative VEGF neutralization activity of test articles is reported relative to the reference standard.

- **Reference Materials:**

  PRS-SB11-01 is the current SB11 primary reference standard (PRS) which was manufactured in September 2019 (b) (4) PRS-SB11-01 was qualified against the clinical reference standard lot RS-SB11-01 using appropriate release, extended characterization and biological activity specifications. RS-SB11-01 was used for release and stability testing of clinical and PPQ DS and DP SB11 lots. PRS-SB11-01 is reserved for the qualification of future SB11 reference standards and is not intended for routine commercial release and stability testing. PRS-SB11-01 will be re-qualified annually using appropriate specifications for pH, protein concentration, charge variants, size variants, and biological activity (VEGF binding and VEGF neutralization relative to working reference standard).

  WRS-SB11-01 is the current SB11 working reference standard (WRS) which was manufactured in June 2020 (b) (4) WRS-SB11-01 was qualified against the current PRS (PRS-SB11-01) using appropriate release, extended characterization and biological activity specifications. WRS-SB11-01 is intended to be used for routine commercial release and stability testing that requires an RS. WRS-SB11-01 will be re-qualified annually using appropriate specifications for pH, protein concentration, charge variants, size variants, and

biological activity (VEGF binding and VEGF neutralization relative to PRS).

PRS and WRS re-qualification results will be plotted for trend analysis to identify potential drifts in product quality that may lead to out-of-specifications (OOS). WRS data generated during routine lot release and stability testing, including potency assay control results tested against WRS, will also be incorporated as part of the WRS trending program. A protocol to support the qualification and re-qualification of future SB11 PRS and WRS lots was provided and is acceptable.

- **Critical starting materials or intermediates:**

(b) (4)

- **Manufacturing process summary:**

(b) (4)

(b) (4)

- **Container closure:**

(b) (4)

- **Dating period and storage conditions**:

The dating period for SB11 DS is (b) (4) months when stored at (b) (4)

C. Drug Product [Byooviz] Quality Summary:

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

The following table provides a summary of the identification, risk, and lifecycle knowledge management for the drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

CQA (type)	Risk	Origin	Control Strategy	Other
Particulate matter (visible and subvisible) (Product or process related impurities)	Safety/immunogenicity	Manufacturing process and container closure system	(b) (4)	N/A
Extractable Volume (general)	Efficacy/dosing	Manufacturing process		N/A

Leachables (process related impurities)	Safety	Manufacturing equipment and container closure	(b) (4)	Long-term leachable study results for the DP container closure system were only available during the review cycle through 12 months at 5 ± 3°C. A post-market commitment will be issued for providing updated study results annually in the BLA Annual Report and to submit the final study report, including the toxicological risk evaluation, to the BLA.
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process		N/A
Endotoxin (Contaminant)	Safety, Purity, Raw materials, manufacturing process	Controlled (b) (4)		N/A
Container closure integrity	Safety (sterility assurance)	Container closure breaches during storage. May be impacted by storage conditions.		N/A

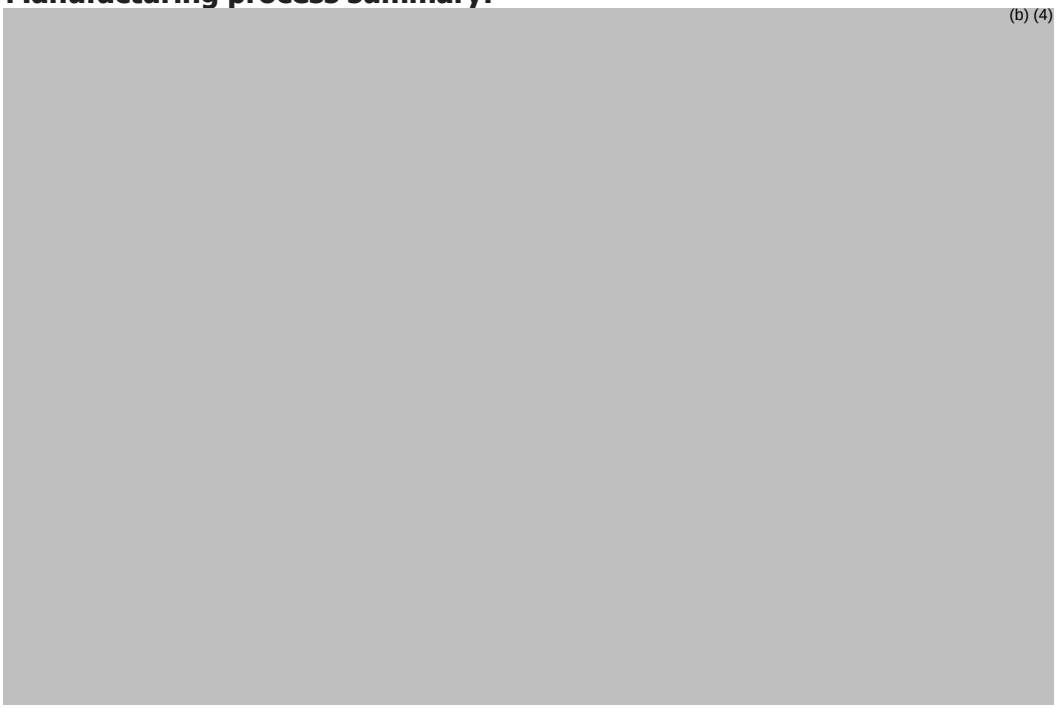
- **Potency and Strength:**
  Byooviz is supplied at a strength of 0.5 mg/0.05 mL (10 mg/mL). Potency is defined as the percent VEGF binding and neutralization activity relative to the current ranibizumab-nuna WRS. The potency assays are the same as described for DS.

- **Summary of Product Design:**
  Byooviz is supplied in a single-dose vial as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution. Byooviz is intended for intravitreal injection using a 5-micron sterile filter needle (19-gauge), 1 mL sterile Luer lock syringe and sterile injection needle (30-gauge). The single-dose

vial contains 0.05 mL deliverable volume (0.5 mg dose) of 10 mg/mL ranibizumab-nuna, 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20 at pH 5.5.

- **List of Excipients:**
  Histidine HCl, α,α-trehalose dihydrate and polysorbate 20 are all compendial excipients.

- **Reference Materials:**
  The same reference material is used for DS and DP.

- **Manufacturing process summary:**
  (b) (4)
  

- **Container closure:**
  The DP container closure system is comprised of a (b) (4) glass vial, 13 mm (b) (4) rubber stopper, and 13 mm (b) (4) flip-off cap.

- **Dating period and storage conditions:**
  The dating period for Byooviz is 30 months when stored at 5 ± 3°C, protected from light.

- **List of co-packaged components, if applicable:** N/A

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall recommendation: *APPROVED*					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture and packaging, QC release testing, In-process testing, MCB and WCB storage	(b) (4)		PLI is required	VAI; 1-item FDA 483	Approved based on PLI
MCB and WCB storage			No evaluation Necessary (NEN)	N/A	N/A
Manufacture of MCB and WCB			No evaluation Necessary (NEN)	N/A	N/A
In-process testing			Acceptable Based on Profile	N/A	Approve
QC release and stability testing			Acceptable Based on Profile	N/A	Approve
QC release and stability testing			Acceptable Based on Profile	N/A	Approve

DS Storage	(b) (4) N/A	No evaluation Necessary (NEN)	N/A	N/A
DS Storage	(b) (4)	No evaluation Necessary (NEN)	N/A	N/A

DRUG PRODUCT

Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture, QC release testing, In-process testing, Bulk DP storage	(b) (4)		The subject filling Line has not yet make any US licensed products and have not been inspected on site by the Agency or any other MRA authorities	VAI; 1-item FDA 483	Approved based on PLI
QC release and stability testing			Approved based on profile and inspectional history	N/A	Approve
QC release and stability testing			Approved based on profile and inspectional history	N/A	Approve
Secondary Packaging			No evaluation Necessary (NEN)	N/A	N/A

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) , proposed for ranibizumab DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- (b) (4) lifetime protocol
- Master cell bank and working cell bank stability protocol
- Primary reference standard and working reference standard qualification and re-qualification protocol
- Post-approval annual stability protocol

ii. Outstanding review issues/residual risk:
- Bioburden test method suitability data for in-process samples from at least one additional lot of SB11 drug substance is requested via a PMC.

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
- Post-approval annual stability protocol

ii. Outstanding review issues/residual risk:
- Long-term real-time leachable evaluation for DP container closure system is requested via a PMC.

iii. Future inspection points to consider: None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIE N WILSON
09/16/2021 03:59:16 PM

QING ZHOU
09/16/2021 04:04:36 PM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 9, 2021
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Jens Fricke, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761202
Applicant:	Samsung Bioepis Co., Ltd.
Submission Date:	September 17, 2020
Product:	Ranibizumab-nuna
Dosage form(s):	injection
Strength and Container-Closure:	0.5 mg/0.05 mL in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	OBP Labeling determined that the prescribing information submitted on August 13, 2021 is not acceptable due to the lack of the dosage form in required parts and sections of the Prescribing Information. Therefore, the Prescribing Information does not comply with 21 CFR 201.57. The container labels and carton labeling submitted on August 13, 2021 were assessed and include areas of needed improvement but were found to be acceptable at this time from an OBP Labeling perspective (see Appendix C).

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

OBP Labeling notes that the dosage form is not provided in some required parts and sections of prescribing information and thus the labeling will not meet regulatory requirements per 21 CFR 201.57(a)(8), 21 CFR 201.57(c)(4), or 21 CFR 201.57(c)(17). The dosage form (injection) is not provided in the following required parts and sections (Highlights Dosage forms and Strengths), FPI section 3 (Dosage forms and Strengths), FPI section 16 (How Supplied Storage and Handling). We note that the PI is formatted similarly to its innovator, Lucentis. OBP Labeling has no other recommended revisions other than to include the customary dosage form in required parts and sections. We note that "Intravitreal injection" is the route of administration and the dosage form for this drug product is "injection".

The container labels and carton labeling submitted on August 13, 2021 were assessed and have areas of needed improvement including inconsistent presentation of the quantitative amount of the active ingredient on the container and carton labeling compared to the appearance provided in key sections of prescribing information where the "strength or potency" is to appear [(Highlights Dosage forms and Strengths), FPI section 3 (Dosage forms and Strengths), FPI section 16 (How Supplied Storage and Handling)]. At this time, we recommend all labeling convey consistent information for the quantitative amount of the active ingredient as an expression of strength per fraction of mL (0.5 mg/0.05 mL). However, container labels and carton labeling submitted on August 13, 2021 were found to be acceptable (see Appendix C) from an OBP Labeling perspective

APPENDICES

Appendix A: Proposed Labeling
Prescribing Information (submitted on September 17, 2020
\\CDSESUB1\evsprod\bla761202\0001\m1\us\draft-labeling-text-highlights-pi-redline.pdf)

Container Labels (submitted on September 17, 2020)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: *The container label submitted by the Applicant initially presented the quantitative amount of active ingredient in the format consistent with other injectable products approved by the CDER/FDA. In the container and carton labeling information request dated August 9, 2021, the Division of Ophthalmology requested that the Applicant revise the quantitative amount of active ingredient from "0.5 mg/0.05 mL" to read "0.5 mg". We defer to DMEPA for medication error concerns related to the presentation of the quantitative amount of active ingredient and any differences in appearance between the proposed revisions by the Division of Ophthalmology on container/carton labeling (0.5 mg) and in the prescribing information (0.05 mL of 10 mg/mL solution). We note that this label meets the regulatory requirements for quantitative amount of active ingredient but does not conform to the consistent approach for FDA approved labeling that follows USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) for labeling of injectable products which states that 'For single-dose and multiple-dose injectable drug products with containers that supply a volume of drug less than 1 mL: The only expression of strength should be strength per fraction of mL' (0.5 mg/0.05 mL).*

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.

Applicant response: Samsung Bioepis confirms that there is no text on the ferrule and cap overseal of the vials, in compliance with the revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located *Applicant response:* (b) (4)

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011	✓ Yes ☐ No

Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic	☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No

	☐ N/A

Comment/Recommendation: If space permits, consider revising storage statement to include units on each value "Refrigerate at 2°C to 8°C (36°F to 46°F). *The Applicant revised as requested*

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the carton contents statement to read as follows: **"CONTENTS:** one Byooviz single-dose vial and one Prescribing Information".

*This recommendation was not implemented as requested because the Division of Ophthalmology requested that the Applicant revise to "**CONTENTS:** Each Byooviz carton contains one 2 mL glass vial of ranibizumab-nuna vial and one package insert". We note that this labeling attempts to meet the regulatory requirements related to providing the number of containers. We defer to DMEPA for medication error concerns related to labeling including the container closure 2 mL vial size which is not important information for the end user with potential for confusion with the total volume of solution (0.05 mL) which is not provided in the presentation of the quantitative amount of active ingredient per the format consistent with other injectable products approved by the CDER/FDA due to the revision requested by the Division of Ophthalmology. We also note that the terminology "package insert" is an outdated terminology not consistent with terminology used for PLR formatted labeling referred to as "Prescribing Information" in 21 CFR 201.57.*

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: *The carton labeling submitted by the Applicant initially presented the quantitative amount of active ingredient in the format consistent with other injectable products approved by the CDER/FDA. In the container and carton labeling information request dated August 9, 2021, the Division of Ophthalmology requested that the Applicant revise the quantitative amount of active ingredient from "0.5 mg/0.05 mL" to read "0.5 mg". We defer to DMEPA for medication error concerns related to the presentation of the quantitative amount of active ingredient and any differences in appearance between the proposed revisions by the Division of Ophthalmology on container/carton labeling (0.5 mg) and in the prescribing information (0.05 mL of 10 mg/mL solution). We note that this labeling meets the regulatory requirements for quantitative amount of active ingredient but does not conform to the consistent approach for FDA approved labeling that follows USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) for labeling of injectable products which states that 'For single-dose and multiple-dose injectable drug products with containers that supply a volume of drug less than 1 mL: The only expression of strength should be strength per fraction of mL' (0.5 mg/0.05 mL).*

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise storage statement to include units on each value as: "**STORAGE:** Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze." *The Applicant revised as requested to include the units on each value.*

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No

	☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No

	☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise from "single-use" to "single-dose". *The Applicant revised as requested*

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the statement of dosage from "Usual Dosage: See Prescribing Information" to read as "Dosage: See Prescribing Information". *The Applicant revised as requested*

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: for biologics, the proper name does not include the dosage form thus it was relocated to appear outside of the parenthesis and a placeholder for the four-letter suffix has been added to the proper name *The Applicant revised as requested*

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☐ Yes ☒ No ☐ N/A

Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: Revised strength presentation to be consistent with your container and carton labeling (0.5 mg/0.05 mL).

This recommendation was not implemented because this proposed revision was not provided to the Applicant by the Division of Ophthalmology. We defer to DMEPA for medication error concerns related to the presentation of the quantitative amount of active ingredient and any differences in appearance between the container/carton labeling which also was a proposed revision by the Division of Ophthalmology (0.5 mg) and in the prescribing information (0.05 mL of 10 mg/mL solution). We note that this product meets the regulatory requirements for quantitative amount of active ingredient but does not conform to the consistent approach for FDA approved labeling that follows USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) for labeling of injectable products which states that 'For single-dose and multiple-dose injectable drug products with containers that supply a volume of drug less than 1 mL: The only expression of strength should be strength per fraction of mL' (0.5 mg/0.05 mL).

Deleted identifying characteristics as they are not required for this Highlight section which provide a concise summary of information *The Applicant revised as requested*

The appropriate package-type term for this product is "single-dose". Revise throughout and across all labels and labeling for consistency. A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. *The Applicant revised as requested*

The Applicant initially submitted proposed labeling that included the customary format and location of the dosage form as "intravitreal injection", which was determined to be acceptable by OBP Labeling and is the format provided for another intravitreal injection drug product approved by the Division of Ophthalmology. We note that based on proposed revisions made by the Division of Ophthalmology to section 3 (Dosage Forms and Strengths) removes the dosage form and this does not comply with 21 CFR 201.57(a)(8). OBP Labeling determines this to be unacceptable and defers to the Division of Ophthalmology and the Office of Therapeutic Biologics and Biosimilars.

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	☐ Yes ☒ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: Revised strength presentation to be consistent with your container and carton labeling. *This recommendation was not implemented because this proposed revision was not provided to the Applicant by the Division of Ophthalmology. We defer to DMEPA for medication error concerns related to the presentation of the quantitative amount of active ingredient and any differences in appearance between the container/carton labeling which also was a proposed revision by the Division of Ophthalmology (0.5 mg) and in the prescribing information (0.05 mL of 10 mg/mL solution). We note that this product meets the regulatory requirements for quantitative amount of active ingredient but does not conform to the consistent approach for FDA approved labeling that follows USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) for labeling of injectable products which states that 'For single-dose and multiple-dose injectable drug products with containers that supply a volume of drug less than 1 mL: The only expression of strength should be strength per fraction of mL' (0.5 mg/0.05 mL).*

Added the clarity of the solution for a complete description of the identifying characteristics of the dosage form provided in the 3.2.P.1 submission (see 21 CFR 201.57(c)(4) *The Applicant revised as requested*

Revised from "single-use" to "single-dose" *The Applicant revised as requested*

The Applicant initially submitted proposed labeling that included the customary format and location of the dosage form as "intravitreal injection", which was determined to be acceptable by OBP Labeling and is the format provided for another intravitreal injection drug product approved by the Division of Ophthalmology. We note that based on proposed revisions made by the Division of Ophthalmology to section 3 (Dosage Forms and Strengths) removes the dosage form and this does not comply with 21 CFR 201.57(c)(4). We note that the dosage form as required per 21 CFR 201.57(c)(4) does not appear in this section, that the labeling is formatted similarly to the innovator and such change may be made if the change is made in Lucentis. OBP Labeling determines this to be unacceptable and defers to the Division of Ophthalmology and the Office of Therapeutic Biologics and Biosimilars.

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: Deleted the proprietary name and dosage form from the first paragraph since this paragraph discusses the drug substance and added a placeholder for the four-letter suffix on the proper name. *This recommendation was not implemented because this proposed revision was not provided to the Applicant by the Division of Ophthalmology. OBP labeling finds this to be inconsistent with the vast majority of therapeutic biologic product labeling but defers to the Division of Ophthalmology for this labeling preference.*

Relocated the dosage form to appear in the paragraph that discusses the drug product *The Applicant revised as requested*

Added the clarity of the solution per 3.2.P.1 submission *The Applicant revised as requested*
Added the route of administration (see 21 CFR 201.57(c)(12) *The Applicant revised as requested*

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	☐ Yes ☒ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised from "single-use" to "single-dose" *The Applicant revised as requested*

Added the color and clarity of the dosage form see 21 CFR 201.57(c)(17) *The Applicant revised as requested*

We note that the dosage form as required per 21 CFR 201.57(c)(17) does not appear in this section. The labeling is formatted similarly to the innovator and such change may be made if the change is made in Lucentis. OBP Labeling determines this to be unacceptable and defers to the Division of Ophthalmology and the Office of Therapeutic Biologics and Biosimilars.

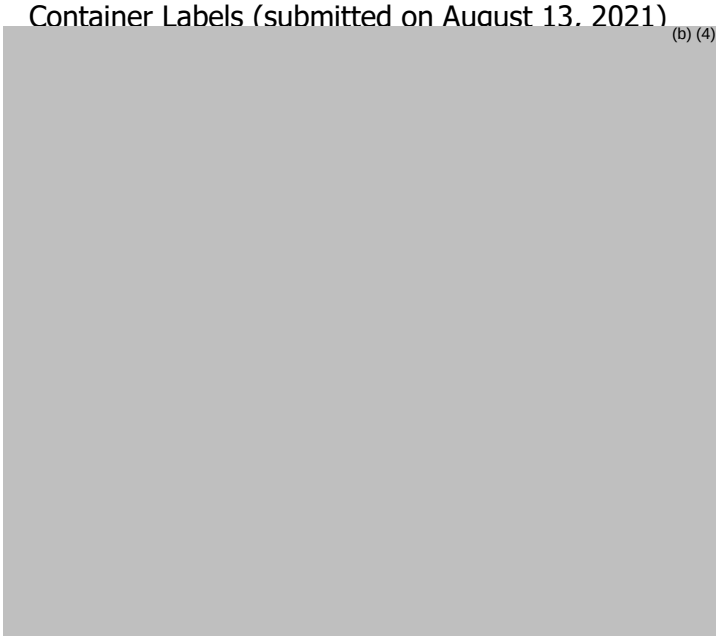
Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation (N/A)
Patient Information Labeling Evaluation (N/A)
Instructions for Use Evaluation (N/A)

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on August 13, 2021
\\CDSESUB1\evsprod\bla761202\0037\m1\us\highlights-pi-byooviz-clean.pdf)
OBP Labeling determined that the prescribing information submitted on August 13, 2021 is not acceptable due to the lack of the dosage form in required parts and sections of the Prescribing Information. Therefore, the Prescribing Information does not comply with 21 CFR 201.57(a)(8), 21 CFR 201.57(c)(4), or 21 CFR 201.57(c)(17).

Container Labels (submitted on August 13, 2021)



1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 9/09/2021 03:22:40PM
GUID: 50814c7000007a3d59329f660d8ddf02

Jens Fricke

Digitally signed by Jens Fricke
Date: 9/13/2021 08:26:06AM
GUID: 57d6a75701b1361db26ba4f78c02a5a9